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## REMARKS

Claims 13-17, 21, 25-29, and 33-37 are now pending. Claims 13-17, 21, 25-29, and 33-37 have been rejected. Claims 13, 33, and 35, and 37 have been amended in this response for clarification purposes.

The Applicants are grateful to the Examiner for the withdrawal of rejections under the first and second paragraph of 35 U.S.C 112 for claims 13-17, 21, and 24-29.

**Introduction**

The method recited by the independent claim 13 is directed to identification of transfecting agents - molecules which are capable of mediating introduction of nucleic acids into cells. Peptoids are promising transfecting agents, but not all peptoids can mediate transfection with good efficiency. A high-throughput library-based method of identifying transfecting peptoids is provided. The method includes the operations of providing a library of peptoids having a general formula I, contacting the peptoids from the library with an oligonucleotide and screening the peptoids for transfection. Significantly, in the provided method, one does not need to know the chemical identity of each individual peptoid ***before*** it is screened for transfection. The peptoids are only identified ***after*** they have been found to be effective transfecting agents. If the peptoid is ineffective for transfection, its sequence does not need to be determined.

The described method provides a cost-effective way of screening large libraries for effective transfection agents, because it eliminates the need for determining and keeping track of the identity of individual peptoids prior to screening.

For example, a library comprising 1,000 different-sequence peptoids encompassed by general formula I can be generated and screened for transfection. In such library, individual peptoids may be attached to a solid support (e.g., beads) prior to screening. While it is known that all of the peptoids in the library are encompassed by the general formula I, the chemical structures of individual peptoids on beads are not known. After a bead is picked from the library pool to be screened for transfection, it is known that it contains one of the peptoids encompassed by the general formula I, but the particular sequence of this peptoid is not known. The peptoids from the library are then screened, and if transfection is observed, those peptoids which were effective for transfection are identified, e.g., sequences of these peptoids are determined using

mass-spectrometry. Thus, if only 10 out of 1,000 peptoids are found to be effective transfecting agents, only 10 peptoid sequences will need to be determined.

The described method provides high efficiency, because libraries in which individual peptoids are unidentified (but encompassed by one general formula) can be generated more easily than libraries in which the exact chemical identity of each individual peptoid is known prior to screening. Thus larger libraries can be obtained, and larger numbers of peptoids can be screened to afford a larger number of hits. This method is significantly different from the methods described in the references that were cited by the Examiner.

The Applicants will now address the various points raised by the Examiner in the Final Office Action.

**Amendments Presented in the Response of June 6, 2006**

The Applicants understand that the claim amendments presented in the response of June 6, 2006 were found by the Examiner to lack clarity. The independent claim 13 recited an operation of providing a library of peptoids having a plurality of unknown sequences and having the general formula I.

The Examiner considers this statement contradictory in that "it is unclear in what sense it is unknown when Formula I recites the sequences of each of the species encompassed by the generic formula I".

The Examiner's subsequent rejections of claims are based on interpretation that peptoids in the library have a ***known*** sequence. Final Office Action, page 9.

However, one cannot fully appreciate the Applicants' claimed invention, without taking into account that the Applicants' library is indeed a library of ***unknown*** peptoids encompassed by the general formula I, and that many of the advantages of the provided method stem from the fact that one need not identify the peptoids in the library prior to screening. The peptoids are unknown in that one knows that all of the peptoids in the library have different sequences encompassed by formula I, but one cannot address a particular sequence to a particular peptoid.

As an analogy, a chemist who did not label identically looking vials containing compounds X, Y, and Z, will not know which compound is contained in each vial after he

accidentally mixes up the vials in a drawer. He will, however, know that these unknown compounds are encompassed by the group of X, Y, and Z.

While the Applicants believe that the language "a library of peptoids having a plurality of unknown sequences and having the general formula I" is clear and unambiguous to one of skill in the art, particularly in light of the specification, in an effort to improve the clarity of claim 13, the Applicants have amended it to recite that "the sequences of individual peptoids in the library are unidentified" when the library is provided. Claim 33 has been similarly amended. These amendments are supported, e.g., by Figure 2.

**Rejections Based on the First Paragraph of 35 U.S.C. 112**

Claims 13-17, 21, 25-29, and 33-37 were rejected under 35 U.S.C 112, first paragraph, as failing to comply with the written description requirement.

1. The Examiner states that "providing a library of peptoids having a plurality of unknown sequences and having the general formula I" is not supported in the specification as filed. The Applicants respectfully submit that this concept is well supported at page 6, paragraph 3, page 8, paragraph 4; page 15, paragraph 3, and in Figure 2 of the instant specification, as was previously noted by the Applicants.

At page 6, paragraph 3, peptoids of formula I are described. At a subsequent page 7, the specification provides a transfection screening method, and further, at page 8, paragraph 3, it is stated that "it will be appreciated that the methods of the invention allow identification of effective peptoids after screening, and does not require that the sequences of the peptoids, e.g., peptoids in a combinatorial library, be known beforehand." Nothing in the intervening text between page 6 and page 8 suggests that the individual peptoids in the library having general formula I need to have identified sequences prior to screening. As will be recognized by those skilled in the art, paragraphs in pages 6-8 are logically linked and do not describe mutually exclusive embodiments. Furthermore, page 15, paragraph 3 provides a detailed description of an example screening method with a reference to Figure 2. Screening involves (a) synthesizing a library of peptoids on beads (an unidentified peptoid x on a bead is shown in Figure 2); (b) placing single beads representing single compounds into wells of a multi-well plate and cleaving compounds from beads; (c) adding oligonucleotides to form complexes; (d) adding peptoid/oligonucleotide complexes to cells; (e) determining whether the cells were transfected; and (f) identifying the peptoids that were effective transfection agents, using, e.g., tandem mass

spectrometry. The described method is one of the preferred embodiments for peptoid screening. Peptoids of formula I are some of the preferred compounds for peptoid libraries to be used in conjunction with provided methods. It is clear that the specification read as a whole describes the use of its preferred compounds in conjunction with its preferred screening method.

2. The Examiner submits that the formula II of claim 33 is not supported in the instant specification. While the generic formula II (which is a subgenus of formula I) is not explicitly disclosed in the specification, it is supported by 64 representative species. These species are shown in Figure 3, and are described at page 17, paragraphs 2-3. All 64 species presented in Figure 3 fall within the scope of the genus of Formula II, and provide written description support for claim 33. It is established, that the genus need not be explicitly recited in the specification, and a claim to a genus can be supported by a representative number of species. For example, *In re Rasmussen*, 650 F.2d 1212 (CCPA 1981), is cited in the M.P.E.P. for the proposition that "there may be situations where one species adequately supports a genus." M.P.E.P. § 2163 (Rev. 3, August 2005), page 2100-182. The court also explicitly stated: "***that a claim may be broader than the specific embodiment disclosed in the specification is in itself of no moment.***" (*Rasmussen*, at 1215; emphasis added). The Applicants respectfully submit that this case is on point, because similarly to *Rasmussen*, the claim is supported not by an explicit recitation of a genus but by a representative number of species.

As it was explained, the Applicants submit that all of the pending claims are fully and clearly supported by the specification as filed, and respectfully request a withdrawal of rejections based on the first paragraph of 35 U.S.C. 112 for claims 13-17, 21, 25-29, and 33-37.

**Rejections Based on the Second Paragraph of 35 U.S.C. 112**

Claims 13-17, 21, 25-29 and 33-37 were rejected under 35 U.S.C 112, first paragraph, as being indefinite.

A. The Examiner submitted that claim 13 is unclear and confusing as to the contradictory statement that library of peptoids has a plurality of unknown sequences and in the same breath has the general formula I. The Applicants have discussed this important point above in the section ***Amendments Presented in the Response of June 6, 2006***. The Applicants believe that the provided explanation and the clarifying amendment, should remove any ambiguity over interpretation of claim 13.

The Examiner also submitted that it in operation (ii) of claim 13 it is "unclear as to how it is determined that a plurality of the unknown peptoids in the library is contacted with the oligonucleotide". The Applicants fail to see why the language describing operation (ii) was considered confusing by the Examiner, but have made an amendment to the possibly clearer language "contacting a plurality of peptoids having unidentified sequences from the library provided in (i) with an oligonucleotide, to form a plurality of peptoid-oligonucleotide mixtures". As it was explained, all of the peptoids in the provided library have unidentified sequences which are encompassed by the general formula I. A plurality of such peptoids is contacted with an oligonucleotide. For example, 50 beads containing different peptoids, each of unidentified sequence, are separately contacted with an oligonucleotide to form 50 different peptoid/oligonucleotide complexes.

B. The Examiner suggests that there is a lack of antecedent basis for the language "said terminal peptoids" in claim 33. The Applicants have amended this claim in their response mailed October 19, 2006 to remove the word "terminal" . Claim 33 now properly depends from claim 13.

The Examiner noted that claim 13 recites "m" within formula I, while claim 33 recites "n" within formula II. "m" is varied between 2 to about 50, while "n" is varied from 2 to 16. In general, the Examiner suggests that formula I of independent claim 13 is inconsistent with formula II of its dependent claim 33.

The Applicants respectfully submit that formula II of dependent claim 33 is a subgenus of formula I of the independent claim 13. The subscript "m" in formula I refers to a number of individual N-derivatized aminoacids within the peptoid sequence. The subscript "n" in formula II refers to a number of ***triads*** of N-derivatized aminoacids within the peptoid sequence. Therefore, "m" and "n" are different and, consequently, have different numerical ranges. Thus, the range for "n" is determined by the range for "m" divided by 3. Further, the definitions of Rb1 and Rb2 as non-cationic moieties in claim 33 are not inconsistent with the definitions given in claim 13, which includes non-cationic substituents such as alkyls.

C. The Examiner submitted that claim 34 "is unclear as to the differences of one cationic moiety, given no structure for said moiety, especially in the base claim, which does not identify said cationic moiety." The Applicants submit that claim 34 properly limits independent claim 13. One skilled in the art will readily recognize that formula I of claim 13 provides moieties which

may be cationic and non-cationic at a physiologically relevant pH. For example, amino and guanidino moieties will be cationic while an alkoxy moiety will be non-cationic. In light of this, it can be seen that a compound comprising two different cationic moieties, can comprise, for example, an amino and a guanidino moiety or two different amino moieties. Because claim 13 recites cationic and non-cationic substituents as it will be apparent to one of skill in the art, claim 34 properly depends from claim 13.

D. Claim 35 was amended in this response to specify that in a method of claim 13, "providing said library comprises synthesizing the library by a mix-and-split protocol". The Applicants submit, that the claim 35 as a whole is not directed to a method of making the library, but specifies the way of providing the library for a method of transfecting agent screening, and therefore further limits claim 13. For example, in the specification at page 15, paragraph 3, a method of screening a library of transfection agents is described, which start by providing a library of peptoids synthesized, in one embodiment, by a mix-and-split protocol. One of skill in the art will understand what steps are involved in a mix-and-split protocol, which is a well-defined method of combinatorial chemistry, and therefore the Applicants believe that a recitation of particular steps for such protocol is not necessary.

E. Claim 36 has been herein amended to recite that the peptoid sequence is determined by tandem mass spectrometry. Support for this amendment is found at page 15, paragraph 3 of the application as filed. The Applicants submit that tandem mass spectrometry is a well-defined method which is known to those of skill in the art of analytical chemistry, and need not be further defined.

**Double Patenting Rejections based on Innis et al.**

The Office Action cites US Patent No. 6,677,445 B1 issued to Innis et al. as the basis for a nonstatutory double patenting rejection of claims 13-17, 21, and 24-29. Specifically, the Office Action mentions claims 1-2 of the Innis patent and also refers to the Innis patent's written description. In claims 1 and 2 of the Innis patent the *compositions* of oligonucleotides and terminal lipitoids are claimed. It is respectfully submitted that the claims to these compositions do not render obvious the claim to a "*method* of identifying peptoids". The Applicants also point out that it is not appropriate to rely on written description of a patent for an obviousness-type double patenting rejection. Only inventions *as claimed* can be evaluated, with the written description serving merely as a dictionary for claim interpretation.

"Any obviousness-type double patenting rejection should make clear:

(A) The differences between the inventions defined by the conflicting claims – a claim in the patent compared to a claim in the application; and

(B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent.

When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art" (MPEP, section 804).

The Examiner states that "the subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: a peptoid-oligonucleotide mixture useful for a method of transfecting a cell." The Applicants, however, point out that the claims of the present patent application are not directed to peptoid-oligonucleotide mixtures at all. The presented claims are directed to a method of identifying transfecting agents in a library of different sequence peptoids. The fact, that the Innis reference claims peptoid-oligonucleotide conjugates in no way renders obvious a method of identifying transfecting agents. Claims of Innis, when read in light of specification, provide no direction whatsoever as to how one would search for transfecting peptoids among a myriad peptoid structures.

Even if, for the sake of argument, one considers the teachings of the Innis specification, he will find no suggestion for screening the libraries of peptoids of general formula I, where individual peptoids have unidentified sequences prior to transfection. Therefore, because the methods of claim 13 are not taught or suggested in the Innis patent, one would not be able to present such claims in the Innis application.

In the "Response to Arguments" the Examiner submits that the method of claim 13 is the obvious use for claimed composition. The Examiner also submits that the Innis patent discloses the composition used in the instant method. The Examiner, however, does not provide the specific paragraphs of the Innis disclosure that teach methods for determining which peptoids are transfecting agents in a library of peptoids having unidentified sequences. The Applicants have reviewed the entire specification of Innis, and have found no indication that such methods are taught or suggested. The Applicants respectfully submit that a particular way of screening the libraries presented in claim 13 is not rendered obvious by the claims of Innis patent which are drawn to particular compositions even when these claims are read in light of specification, at least because the specification does not teach or suggest library screening methods.

The *claimed* invention of the Innis patent does not render obvious the invention defined in the claims of the present application. The Applicants, therefore, respectfully request withdrawal of the double patenting rejection for claims 13-17, 21, and 24-29.

**Rejections based on 35 USC 102(e)**

Claim 33 was rejected under 35 U.S.C 102 (e) as being anticipated by Liotta et al. (USP 6,153,596). The Applicants note that the Examiner interprets claim 33 as describing the method of transfecting a cell with peptoids of formula II. Claim 33, however, is not directed to a method of transfection. It is directed to a method of ***identifying transfecting agents***. Such method is an identification method, based on a particular way of library screening, and is substantially different from the methods found in Liotta.

The claimed method is directed to efficient identification of transfecting agents in a library. Liotta's teachings, however, do not describe library screenings as provided in claim 33. In this regard, it is important to consider that claim 33 provides a library of peptoids having the general formula II, in which the structures of individual peptoids are unidentified prior to screening. Such a method provides a cost-efficient way of generating and screening very large libraries, because identification of peptoids is carried out only after the screening, e.g., only for successful transfecting peptoids but not for each peptoid of the library. The Applicants submit that this argument is commensurate with the scope of the claim, because the claim recites "[a] method of identifying peptoids which are effective in transfecting a cell with an oligonucleotide" and the argument recites particular advantages associated with the identification method as

claimed. In particular, the claim recites providing a library of peptoids having the general formula II, wherein the sequences of individual peptoids in the provided library are unidentified prior to transfection screening. Liotta does not teach a method having operations of claim 33, at least because Liotta does not provide libraries of peptoids encompassed by general formula II, in which individual peptoids in the library have unidentified sequences prior to transfection screening.

In no instance does Liotta disclose such a screening method. Accordingly, the Applicants respectfully request withdrawal of the 102(e) rejections of claim 33.

**Rejections based on 35 USC 103(a)**

Claims 13-17, 21 and 25-29, 33-34 and 36-37 were rejected under 35 USC 103(a) as being unpatentable over Liotta (USP 6,153,596) in view of Murphy (PNAS). The Applicants submit that these claims, are not rendered obvious to one skilled in the art by a combination of Liotta and Murphy references, at least because neither Liotta nor Murphy teach screening of libraries in which individual peptoids have unidentified sequences.

Both Liotta and Murphy are using peptoids of *pre-identified* sequences for cell transfection. In other words, in their methods a peptoid having a precisely known identity is contacted with an oligonucleotide and subsequently with a cell to effect transfection. In the method of claim 13, however, the chemical identity (sequence) of each individual peptoid is not known before it is contacted with an oligonucleotide and a cell. It is only known that it has a sequence encompassed by general formula I, but its particular sequence is not known. Only after the transfection is complete, the sequence of this peptoid is determined. e.g., by tandem mass-spectrometry. The method of claim 13 is a cost-effective method of identifying transfecting agents because it requires less resources directed to identification of peptoid sequences.

The Applicants submit that because the method of claim 1 is directed to identification of transfecting agents, the Applicants' arguments provided in the response mailed June 6, 2006 are fully commensurate in scope with the claims. The arguments clarify that because the method of claim 13 does not require pre-identification of peptoids in the library, much larger libraries can be provided and more efficient screening can be performed, compared to methods of Murphy and Liotta. These arguments will be reiterated herein. The Applicants believe that in view of the

explanations provided in this response and in view of the clarifying claim amendments, the wording of claim 13 is now fully clear and the arguments can be better appreciated.

As it was stated, the Applicants provide a plurality of peptoids of *unidentified* sequences having general formula I, then screen for cell transfection, and only upon successful transfection determine the chemical identity of the transfecting peptoid. The importance of this unobvious distinction will be immediately appreciated by one skilled in the art of drug discovery.

It should be noted that the Applicants' invention as described in the specification is directed towards a transfecting agent identification (discovery) method. As a discovery method it is substantially different from the methods of Liotta and Murphy. It is well understood in the art that a drug discovery process may rely on rational design, a combinatorial library approach, or some combination of the two. This equally applies to a transfection agent discovery process. A discovery process usually involves two distinct components – lead generation and lead optimization. For lead generation, very few rational considerations exist and the library should comprise as many compounds as possible. Lead optimization, on the other hand, has a stronger rational design emphasis, and the library need not be as expansive as in the case for lead generation. Distinct classes of combinatorial libraries, relying on distinct synthetic methods are used in each case.

In rational design methods, some hypothesis is driving the synthesis of defined structures with particular structural properties. The resulting molecules are then tested for activity. For instance, Liotta's hypothesis is that effective transfecting peptoids should have similar size to oligonucleotides, and that they should be able to neutralize or substantially neutralize the oligonucleotide to be transfected. Based on this hypothesis, he proposes to synthesize a library of peptoids with defined size, charge, and structure. In fact, it is critical to know the chemical identity of the peptoid *before* transfection in order to practice Liotta's invention. The library described in Liotta's reference is a rationally designed library of known peptoids. The library described in Murphy is also a library of known-sequence peptoids albeit with a less pronounced emphasis on rational design. It is well known in the art, that libraries of known compounds can be synthesized by parallel synthesis. Parallel synthesis is known to be a rather inefficient combinatorial approach, leading to no more than several hundred compounds in a library. These libraries are suited for lead optimization purposes, but they are not useful for *discovering* leads and identifying *non-designed* effects.

For such a purpose a more expansive library is needed which could comprise thousands or millions of different sequence peptoids, for example. This type of library can be obtained by combinatorial methods other than parallel synthesis, which are not disclosed in the Liotta or Murphy references. As described in the Applicants' specification, this type of library can be synthesized by, for example, a mix-and-split protocol. A mix-and-split approach may lead to millions of combinatorially synthesized peptoids of different and *unidentified* sequences. The sequences of peptoids are unknown because the beads containing individual peptoids are mixed during the synthetic procedure. This protocol is superior to parallel synthesis in its efficiency of generating multiple compounds. Such a library of unknown peptoids is well suited for identification of undesigned effects, e.g., for transfection of a cell type that has not been successfully transfected before. This type of library is not described in Liotta's and Murphy's references and cannot be attained by their synthetic procedures.

In conclusion, the claimed method is more efficient in identifying new transfecting agents because it allows use of easier generated libraries, and requires less peptoid structure determination.

For at least these reasons, the Applicants respectfully submit that the method claimed in claim 13 is not an obvious variation of Liotta's and Murphy's methods, and withdrawal of the 103(a) rejection for claim 13 and its dependent claims 14-17, 21 and 25-29, 33-34, and 36-37 is respectfully requested.

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CONCLUSION

In light of the foregoing remarks, Applicants respectfully submit that all pending claims are in condition for allowance. Thus, Applicants respectfully request a Notice of Allowance from the Examiner. Should any unresolved issues remain, the Examiner is encouraged to contact the undersigned at the telephone number (510) 663 1100.

If any additional fees not submitted with this filing are due in connection with the filing of this Response, the Commissioner is hereby authorized to charge such fees to Deposit Account 500388 (Order No. CHIRP053).

Respectfully submitted,
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